

Appl. No. : **10/063,685**
Filed : **May 8, 2002**

REMARKS

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have cancelled Claims 9, 10 and 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-8, 11-12, and 14 to remove reference to the Figures. Claims 1-6, and 14 have been amended to remove reference to the extracellular domain. Claims 1-5 have been amended to add the limitation that the claimed nucleic acids are more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or normal kidney tissue respectively, or encode a polypeptide that is more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or normal kidney tissue respectively. Claim 14 has been amended to specify the conditions under which hybridization occurs. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claim 14 can be found in the definition of stringent conditions in paragraph [0227] of the specification.

Claims 1-8, 11-14, and 16-20 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 3, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

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Specification:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a "Sequence Listing" as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the "Sequence Listing," which is also submitted herewith.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 17, 2002. Applicants submit herewith more detailed information regarding the cited sequences (attached as Exhibit 1).

Priority Determination:

The PTO has stated that because the claimed nucleotide has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 4, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/098749 filed 9/1/1998.

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Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 29 and 30 were first disclosed in US Provisional Application 60/098749 filed 9/1/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8-10 and 14-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase “the extracellular domain” as PRO831 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of “the extracellular domain”, “lacking its associated signal sequence” because a signal sequence is not generally considered part of an extracellular domain. Applicants have amended Claims 1-6 and 14 to delete any reference to an extracellular domain.

The PTO also objects to the use of “hybridize” and “stringent conditions” since what hybridizes depends on the conditions under which the hybridization is carried out, and “stringent conditions” is a relative term. Applicants have amended Claims 14 and 16 to specify the conditions under which the hybridization occurs. Thus, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO831. One of the asserted utilities for the claimed nucleic acids is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO831 cDNA is more highly expressed in normal lung tissue and kidney tumor compared to lung tumor and normal kidney tissue, respectively. The PTO has rejected this utility because there is no supporting evidence to indicate that the polypeptide encoded by the claimed nucleic acids of the instant invention is more highly expressed in some normal and tumor tissue compared to their tumor and normal counterparts. The PTO also asserts that the evidence that the polynucleotide is

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more highly expressed in kidney tumor and normal lung is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to normal kidney and lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the polynucleotides for diagnostic or therapeutic purposes. Also, the PTO argues that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two. The PTO also states that the specification does not disclose a correlation between any specific disorder and the altered level of the claimed nucleic acids encoding the polypeptides. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added.)

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Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO831 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO831 polypeptide in normal lung and kidney tumor compared to lung tumor and normal kidney tissue is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to normal kidney and lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is

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malignant, is not described. Applicants also address the PTO's argument that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two, and that because cancerous tissue is aneuploid, the data is unreliable. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids related to the gene encoding the PRO831 polypeptide.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding

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polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.”

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, “a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid.” Office Action at 8. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the claimed nucleic acids, or their corresponding polypeptides, whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO831 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in kidney tumor and normal lung compared to normal kidney tissue and lung tumor, respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO acknowledges that if the PRO831 protein has utility, then this confers utility on the polynucleotide encoding the protein. Office Action at 7. However, the PTO argues that there is no supporting evidence that the polypeptide encoded by the polynucleotide of the instant invention is more highly expressed in the kidney tumor compared to the normal kidney tissue and the normal lung tissue compared to the lung tumor tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the polynucleotides encoding PRO831 can be used in cancer diagnosis or therapy.

Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased

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expression of a gene or mRNA expression on the other. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO831 in kidney tumor compared to the normal kidney tissue and normal lung tissue compared to lung tumor tissue. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 3). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide

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expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment.” The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that “such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.” (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO831 mRNA is expressed at a higher level in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue, the PRO831 polypeptide will also be expressed at a higher level in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. As the PTO has acknowledged, “if the protein has utility, then this confers utility upon the polynucleotide....” Thus, Applicants submit that they have established that it is more likely than

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not that one of skill in the art would recognize the asserted utility of the PRO831 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

Applicants submit that they have therefore established two separate basis for utility of the claimed nucleic acids. The first argument is based on the differential expression of the PRO831 encoding gene in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue. The second argument is based on the utility of the PRO831 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. As the PTO acknowledges, the utility of the polypeptide confers utility on the encoding gene as well.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO831, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 3, Mr. Grimaldi explains that:

However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 6). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the

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amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO831. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO831 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO831 polypeptide is more highly expressed in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue. These data are strong evidence that the gene encoding the PRO831 polypeptide is associated with kidney and lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO831 with a specific disease. This is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO831 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and

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protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO831 gene in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue, are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO831 gene is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO831 protein has utility as a diagnostic tool for cancer, and as the PTO acknowledges, nucleic acids encoding the polypeptide also have utility as a result.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO831. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO831 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof

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of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a “reasonable” confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO831 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. The PTO also states that even if a specific and substantial utility were established, they are enabled only for polynucleotides of SEQ ID NO: 29 and fragments that are usable as hybridization probes, they are not enabled for claims to polynucleotides with 80-99% sequence identity to SEQ ID NO: 29, those which encode polypeptides with 80-99% sequence identity to SEQ ID NO: 30, or those which hybridize to any of the above because there is no structural or functional information provided in the specification. The PTO states that there is insufficient guidance regarding how to make PRO831 polynucleotide variants. The PTO also states that the hybridization claims are not enabled because they do not recite that the polynucleotide encodes a protein having a specifically disclosed activity. The PTO next asserts that even if utility of the claimed nucleic acids as hybridization probes is established, degenerate sequences are not enabled.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

The PTO asserts that even with an established utility, only polynucleotides of SEQ ID NO: 29 are enabled because there is no structural or functional information provided. Applicants have amended the claims to incorporate the limitation that the claimed nucleic acids with less than 100% identity to SEQ ID NO: 29, or which encode a protein with less than 100% identity to

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SEQ ID NO: 30, must be more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or normal kidney tissue respectively, or encode a polypeptide that is more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or normal kidney tissue respectively. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

Applicants respectfully disagree that the hybridization claims are not enabled. First, Applicants assert that those of skill in the art are well aware of which sequences will hybridize under various hybridization conditions. This is especially true as Applicants have amended the claims to include specific conditions under which the claimed hybridization occurs. Applicants submit that by disclosing the sequence of the target nucleic acid along with the specific hybridization conditions, Applicants have disclosed sufficient structural information about the claimed nucleic acids such that those of skill in the art would know how to make them. Second, Applicants submit that undue experimentation would not be required to use the claimed nucleic acids as diagnostic tools. The level of skill in the art is high, and methods of using nucleic acid sequences as probes are well-known and well-established in the art. One of skill in the art would know how to use the claimed nucleic acids, for example, as hybridization probes for the diagnosis of cancer as outlined in the specification at, for example, paragraph [0336], and Example 18 beginning at paragraph [0529].

Finally, Applicants note that because they have established a utility for the PRO831 polypeptide, supported by the declarations of two experts in the field, polynucleotides which encode the PRO831 polypeptide also have utility. This includes degenerate polynucleotide sequences which encode the PRO831 polypeptide. Therefore, contrary to the PTO's assertion, polynucleotides that differ from SEQ ID NO: 29 due to codon degeneracy are enabled.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejection of Claims 1-5 and 15-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polynucleotides encode a particular protein, or that any encoded protein possess any particular biological activity, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure “reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter.” *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant’s disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the amended claims, concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO: 29, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO: 30, and as amended, with the functional recitation: “wherein said isolated nucleic acid is more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or

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normal kidney tissue respectively, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal lung tissue or kidney tumor compared to lung tumor or normal kidney tissue respectively". Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO: 29, or polynucleotides which encode a polypeptide of SEQ ID NO: 30, under the specified stringent conditions. Based on the detailed description of the cloning and expression of variants of PRO831 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 29 and 30, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(e) – Anticipation

The PTO rejects Claims 1-19 as anticipated under 35 U.S.C. § 102(e) by Ryan *et al.* (U.S. Patent No. 6,399,349) (hereinafter Ryan), which was filed September 2, 1998 and issued on June 4, 2002. The PTO states that Ryan discloses a sequence, SEQ ID NO: 4, that has 100% identity to polynucleotides of SEQ ID NO: 29 of the instant invention from 1518-1052, a length of 467 nucleotides. The PTO argues that this meets the limitations of claims 1-16 in that it provides the nucleotide which is identical to SEQ ID NO: 29 and could encode the various regions described in the instant invention. The PTO also argues that given this identity, the sequence of Ryan would hybridize under stringent conditions to SEQ ID NO: 29. Finally, the PTO states that Ryan also describes vectors and host cells meeting the limitations of claims 17-19. Applicants respectfully traverse.

As discussed above, Applicants claim priority to US Provisional Application 60/098749 filed 9/1/1998. The sequences of SEQ ID NOs: 29 and 30 were first disclosed in US Provisional Application 60/098749 filed 9/1/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Applicants are entitled to priority to U.S. Provisional Application No. 60/098749 filed on **September 1, 1998**. This application includes the disclosure of the full length sequence of SEQ

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ID NOS: 29 and 30. As the September 1, 1998 date precedes the date of Ryan, September 2, 1998, Applicants have shown possession of the claimed invention prior to Ryan.

The well-established “Stempel Doctrine” stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his “invention”.

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (*Id.* at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show

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that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited references. Ryan discloses the complement of a portion of SEQ ID NO: 29. Ryan's disclosure is buried in a 50,000 nucleotide sequence (SEQ ID NO: 4) which is part of a total sequence that is 206,954 nucleotides long. Ryan states only that the 150,000 nucleotides of SEQ ID NOs: 3, 4, and 5, "represent sequences upstream of the AmP coding region." Ryan at column 12, lines 2-4. Thus, Ryan discloses nothing more than the complement of a portion of SEQ ID NO: 29. Applicants demonstrated, by means of the disclosure in their provisional application filed September 1, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO: 29, as disclosed in the Ryan reference dated September 2, 1998. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102 be withdrawn.

Even if Ryan were available as prior art, it does not anticipate Claims 1-19. First, Claim 11 is not anticipated because Ryan does not disclose the entirety of SEQ ID NO: 29. Second, to anticipate under 35 U.S.C. § 102, "the reference must also enable one of skill in the art to make and use the claimed invention." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001). As discussed above, Ryan only discloses the complement of a portion of the sequence in question buried in a sequence that is 206,954 nucleotides long, and simply identifies it as being upstream of the AmP coding region. This disclosure in no way enables one to make and use the claimed invention. Thus, even if Ryan were available as prior art, which it is not, it does not anticipate the claimed invention. Applicants therefore respectfully request that the rejection under 35 USC §102(e) be withdrawn.

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Rejection under 35 U.S.C. §103(a) – Obviousness

The PTO rejects Claim 20 under 35 U.S.C. § 103(a) as unpatentable over Ryan *et al.* in view of Sambrook *et al.* The PTO asserts that although Ryan expresses the DNA in various host cells, including cos-1 cells, they do not teach the expression in CHO cells, E. coli and yeast cell. The PTO asserts that Sambrook discloses expression of proteins in mammalian and E. coli cells. The PTO concludes that it would have been obvious to one of skill in the art to combine the teaching of Ryan with that of Sambrook.

As discussed above in the rejection under 35 U.S.C. § 102(e), Applicants are entitled to priority to U.S. Provisional Application No. 60/098749 filed on September 1, 1998. This application includes the disclosure of the full length sequence of SEQ ID NOS: 29 and 30. As the September 1, 1998 date precedes the date of the Ryan reference, September 2, 1998, Applicants have shown possession of the claimed invention prior to the Ryan reference. Thus, Applicants respectfully submit that the Ryan reference is not available as prior art, and request that the rejections under 35 USC §103(a) be withdrawn.

Even if Ryan is available as prior art, as discussed above, Ryan discloses no more than the complement of a portion of the SEQ ID NO: 29 buried in a sequence that in total is 206,954 nucleotides long. It would not have been obvious to one of skill in the art to take the complement of a 495 nucleotide portion of that sequence, subclone it into a vector, and express it in a host cell. There is absolutely no motivation for one of skill in the art to choose the disclosed sequence of SEQ ID NO: 29 for expression in the absence of the disclosure in the instant application. Thus, even if Ryan were available as prior art, which it is not, it would not make Claim 20 of the instant application obvious. Applicants therefore respectfully request that the rejection under 35 USC §103(a) be withdrawn.

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CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 2, 2004

By: 

AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

S:\DOCS\BSG\BSG-1341.DOC
080504

GenBank (Release 142, jun 2004)

494 100 0.0

P_AAF92072 Human PRO831 cDNA. 494 bp, cDNA, PAT 15-MAY-2001

ACCESSION P_AAF92072

KEYWORDS GENESEQ; Human; PRO protein; mapping; patent; patentdb (v200414, 01-JUL-2004).

SOURCE Homo sapiens.

ORGANISM Homo sapiens.

REFERENCE 1 (bases 1 to 494)

AUTHORS Eaton,D.L., Filvaroff,E., Gerritsen,M.E., Goddard,A.,
Godowski,P.J. Grimaldi,C.J., Gurney,A.L., Watanabe,C.K.,
Wood,W.I.

TITLE Eighty four nucleic acids encoding PRO polypeptides, useful in
molecular biology, including use as hybridization probes, and in
chromosome and gene mapping.

JOURNAL Patent: WO200116318-A2; Filing Date: 24-AUG-2000; 2000WO-US023328;
Publication Date: 08-MAR-2001; Priority: 01-SEP-1999;
99WO-US020111. 15-SEP-1999; 99WO-US021090. 07-DEC-1999;
99US-0169495P. 09-DEC-1999; 99US-0170262P. 11-JAN-2000;
2000US-0175481P. 18-FEB-2000; 2000WO-US004341. 18-FEB-2000;
2000WO-US004342. 22-FEB-2000; 2000WO-US004414. 01-MAR-2000;
2000WO-US005601. 03-MAR-2000; 2000US-0187202P. 21-MAR-2000;
2000US-0191007P. 30-MAR-2000; 2000WO-US008439. 25-APR-2000;
2000US-0199397P. 22-MAY-2000; 2000WO-US014042. 05-JUN-2000;
2000US-0209832P; Assignee: (GETH) GENENTECH INC; Cross Reference:
WPI; 2001-183260/18. P-PSDB; AAB87540; Patent Format: Claim 2; Fig
29; 278pp; English.

COMMENT The present sequence is the coding sequence for a human PRO
polypeptide (secreted and transmembrane). The PRO protein, and PRO
agonists, PRO antagonists or anti-PRO antibodies are useful for
preparation of a medicament useful in the treatment of a condition
which is responsive to the PRO protein, agonists, antagonists or
anti-PRO antibodies. The PRO protein may also be employed as
molecular weight markers for protein electrophoresis. The PRO
coding sequence has applications in molecular biology, including
use as hybridisation probes, and in chromosome and gene mapping

FEATURES Location/Qualifiers

BASE COUNT 128 a 111 c 120 g 135 t

ORIGIN

494 100 0.0

AX092298 Sequence 29 from Patent WO0116318. 494 bp,
DNA, linear, PAT 21-MAR-2001

ACCESSION AX092298

VERSION AX092298.1 GI:13444463

KEYWORDS

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1

AUTHORS Eaton,D.L., Filvaroff,E., Gerritsen,M.E., Goddard,A.,
Godowski,P.J., Grimaldi,C.J., Gurney,A.L., Watanabe,C.K. and
Wood,W.I.

TITLE Secreted and transmembrane polypeptides and nucleic acids encoding
the same

JOURNAL Patent: WO 0116318-A 29 08-MAR-2001;
Genentech, Inc. (US)

FEATURES Location/Qualifiers
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BASE COUNT
ORIGIN

493 100 0.0
P_AAA37028 Human PRO831 (UNQ471) cDNA sequence SEQ ID NO:21. 493 bp,
cDNA, PAT 08-AUG-2000

ACCESSION P_AAA37028

KEYWORDS GENESEQ; Human; PRO polypeptide; membrane bound protein; receptor;
diagnosis; transmembrane; secretion; immunoadhesion; pharmaceutical;
screening; patent; patentdb (v200414, 01-JUL-2004).

SOURCE Homo sapiens.
ORGANISM Homo sapiens.

REFERENCE 1 (bases 1 to 493)

AUTHORS Baker,K., Goddard,A., Gurney,A.L., Smith,V., Watanabe,C.K.,
Wood,W.I.

TITLE New mammalian DNA sequences encoding transmembrane, receptor or
secreted PRO polypeptides, useful for screening of potential
peptide or small molecule inhibitors of the relevant
receptor/ligand interactions.

JOURNAL Patent: WO200012708-A2; Filing Date: 01-SEP-1999; 99WO-US020111;
Publication Date: 09-MAR-2000; Priority: 01-SEP-1998;
98US-0098716P. 01-SEP-1998; 98US-0098749P. 01-SEP-1998;
98US-0098750P. 02-SEP-1998; 98US-0098803P. 02-SEP-1998;
98US-0098821P. 02-SEP-1998; 98US-0098843P. 09-SEP-1998;
98US-0099536P. 09-SEP-1998; 98US-0099596P. 09-SEP-1998;
98US-0099598P. 09-SEP-1998; 98US-0099602P. 09-SEP-1998;
98US-0099642P. 10-SEP-1998; 98US-0099741P. 10-SEP-1998;
98US-0099754P. 10-SEP-1998; 98US-0099763P. 10-SEP-1998;
98US-0099792P. 10-SEP-1998; 98US-0099808P. 10-SEP-1998;
98US-0099812P. 10-SEP-1998; 98US-0099815P. 10-SEP-1998;
98US-0099816P. 15-SEP-1998; 98US-0100385P. 15-SEP-1998;
98US-0100388P. 15-SEP-1998; 98US-0100390P. 16-SEP-1998;
98US-0100584P. 16-SEP-1998; 98US-0100627P. 16-SEP-1998;
98US-0100661P. 16-SEP-1998; 98US-0100662P. 16-SEP-1998;
98US-0100664P. 17-SEP-1998; 98US-0100683P. 17-SEP-1998;
98US-0100684P. 17-SEP-1998; 98US-0100710P. 17-SEP-1998;
98US-0100711P. 17-SEP-1998; 98US-0100919P. 17-SEP-1998;
98US-0100930P. 18-SEP-1998; 98US-0100848P. 18-SEP-1998;
98US-0100849P. 18-SEP-1998; 98US-0101014P. 18-SEP-1998;
98US-0101068P. 18-SEP-1998; 98US-0101071P. 22-SEP-1998;
98US-0101279P. 23-SEP-1998; 98US-0101471P. 23-SEP-1998;
98US-0101472P. 23-SEP-1998; 98US-0101474P. 23-SEP-1998;
98US-0101475P. 23-SEP-1998; 98US-0101476P. 23-SEP-1998;
98US-0101477P. 23-SEP-1998; 98US-0101479P. 24-SEP-1998;
98US-0101738P. 24-SEP-1998; 98US-0101741P. 24-SEP-1998;
98US-0101743P. 24-SEP-1998; 98US-0101915P. 24-SEP-1998;
98US-0101916P. 29-SEP-1998; 98US-0102207P. 29-SEP-1998;
98US-0102240P. 29-SEP-1998; 98US-0102307P. 29-SEP-1998;
98US-0102330P. 29-SEP-1998; 98US-0102331P. 30-SEP-1998;
98US-0102484P. 30-SEP-1998; 98US-0102487P. 30-SEP-1998;

98US-0102570P. 30-SEP-1998; 98US-0102571P. 01-OCT-1998;
 98US-0102684P. 01-OCT-1998; 98US-0102687P. 02-OCT-1998;
 98US-0102965P. 06-OCT-1998; 98US-0103258P. 06-OCT-1998;
 98US-0103449P. 07-OCT-1998; 98US-0103314P. 07-OCT-1998;
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 98US-0103395P. 07-OCT-1998; 98US-0103396P. 07-OCT-1998;
 98US-0103401P. 08-OCT-1998; 98US-0103633P. 08-OCT-1998;
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 98US-0103711P. 14-OCT-1998; 98US-0104257P. 20-OCT-1998;
 98US-0104987P. 20-OCT-1998; 98US-0105000P. 20-OCT-1998;
 98US-0105002P. 21-OCT-1998; 98US-0105104P. 22-OCT-1998;
 98US-0105169P. 22-OCT-1998; 98US-0105266P. 26-OCT-1998;
 98US-0105693P. 26-OCT-1998; 98US-0105694P. 27-OCT-1998;
 98US-0105807P. 27-OCT-1998; 98US-0105881P. 27-OCT-1998;
 98US-0105882P. 27-OCT-1998; 98US-0106062P. 28-OCT-1998;
 98US-0106023P. 28-OCT-1998; 98US-0106029P. 28-OCT-1998;
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 98US-0106033P. 28-OCT-1998; 98US-0106178P. 29-OCT-1998;
 98US-0106248P. 29-OCT-1998; 98US-0106384P. 29-OCT-1998;
 98US-0108500P. 30-OCT-1998; 98US-0106464P. 03-NOV-1998;
 98US-0106856P. 03-NOV-1998; 98US-0106902P. 03-NOV-1998;
 98US-0106905P. 03-NOV-1998; 98US-0106919P. 03-NOV-1998;
 98US-0106932P. 03-NOV-1998; 98US-0106934P. 10-NOV-1998;
 98US-0107783P. 17-NOV-1998; 98US-0108775P. 17-NOV-1998;
 98US-0108779P. 17-NOV-1998; 98US-0108787P. 17-NOV-1998;
 98US-0108788P. 17-NOV-1998; 98US-0108801P. 17-NOV-1998;
 98US-0108802P. 17-NOV-1998; 98US-0108806P. 17-NOV-1998;
 98US-0108807P. 17-NOV-1998; 98US-0108867P. 17-NOV-1998;
 98US-0108925P. 18-NOV-1998; 98US-0108848P. 18-NOV-1998;
 98US-0108849P. 18-NOV-1998; 98US-0108850P. 18-NOV-1998;
 98US-0108851P. 18-NOV-1998; 98US-0108852P. 18-NOV-1998;
 98US-0108858P. 18-NOV-1998; 98US-0108904P; Assignee: (GETH)
 GENENTECH INC; Cross Reference: WPI; 2000-237871/20. P-PSDB;
 AAY99346; Patent Format: Claim 2; Fig 13; 773pp; English.

COMMENT

AAA37022 to AAA37144 encode the new isolated human transmembrane,
 receptor or secreted PRO polypeptides given in AAY99340 to AAY99462.
 The transmembrane and receptor PRO proteins can be used for
 screening of potential peptide or small molecule inhibitors of the
 relevant receptor/ligand interactions. The polypeptides and
 nucleotide sequences encoding then have various industrial
 applications, including uses as pharmaceutical and diagnostic
 agents. AAA37145 to AAA37330 represent PCR primers and
 hybridisation probes used in the isolation of the PRO polypeptides
 from the present invention

FEATURES

Location/Qualifiers

BASE COUNT 127 a 111 c 120 g 135 t
 ORIGIN

486 100 0.0

BC021104 Homo sapiens apelin, AGTRL1 ligand, mRNA (cDNA clone MGC:31846
 IMAGE:4586949), complete cds. 2673 bp,
 mRNA, linear, PRI 30-JUN-2004

ACCESSION BC021104

VERSION BC021104.1 GI:18088893

KEYWORDS MGC.

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 2673)

AUTHORS Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F.,
Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L.,
Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S.,
Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J.,
Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J.,
McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W.,
Villalón,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A.,
Fahey,J., Helton,E., Kettelman,M., Madan,A., Rodrigues,S.,
Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M.,
Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
Schnierch,A., Schein,J.E., Jones,S.J. and Marra,M.A.

TITLE Generation and initial analysis of more than 15,000 full-length
human and mouse cDNA sequences

JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)

REFERENCE 2 (bases 1 to 2673)

AUTHORS Strausberg,R.

TITLE Direct Submission

JOURNAL Submitted (03-JAN-2002) National Institutes of Health, Mammalian
Gene Collection (MGC), Cancer Genomics Office, National Cancer
Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590,
USA

REMARK NIH-MGC Project URL: <http://mgc.nci.nih.gov>

COMMENT Contact: MGC help desk

Email: cgapbs-r@mail.nih.gov

Tissue Procurement: DCTD/DTP

cDNA Library Preparation: Rubin Laboratory

cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)

DNA Sequencing by: Genome Sequence Centre,

BC Cancer Agency, Vancouver, BC, Canada

info@bcgsc.bc.ca

Steve Jones, Sarah Barber, Mabel Brown-John, Yaron Butterfield,
Andy Chan, Steve S. Chand, William Chow, Alison Cloutier, Ruth
Featherstone, Malachi Griffith, Obi Griffith, Ran Guin, Nancy Liao,
Kim MacDonald, Amara Masson, Mike R. Mayo, Josh Moran, Ryan Morin,
Teika Olson, Diana Palmquist, Anca Petrescu, Anna Liisa Prahbu,
Parvaneh Saeedi, JR Santos, Angelique Schnierch, Ursula Skalska,
Duane Smailus, Jeff Stott, Miranda Tsai, George Yang, Jacquie
Schein, Asim Siddiqui, Rob Holt, Marco Marra.

Clone distribution: MGC clone distribution information can be found
through the I.M.A.G.E. Consortium/LLNL at: <http://image.llnl.gov>

Series: IRAL Plate: 40 Row: f Column: 18

This clone was selected for full length sequencing because it
passed the following selection criteria: matched mRNA gi: 21314667.

FEATURES Location/Qualifiers

source

1..2673

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BASE COUNT
ORIGIN
468 100   0.0
P_AAX235184 Human kidney aminopeptidase P genomic DNA fragment 2. 998 bp,
          DNA, PAT 23-JUN-1999
ACCESSION   P_AAX23518
KEYWORDS    GENESEQ; Aminopeptidase; human; AmP; gene therapy; treatment;
          AmP-deficiency; prenatal diagnosis; angioedema; antihypertensive
          agent; atherosclerosis; arterial stenosis; industrial protein feed;
          malabsorption syndrome; proteinaceous waste degradation; additive;
          immunohistochemistry; patent; patentdb (v200414, 01-JUL-2004).

SOURCE      Homo sapiens.
ORGANISM    Homo sapiens.
REFERENCE   1 (bases 1 to 49998)
AUTHORS     Ryan, J.W., Sprinkle, T.J.C., Venema, R.C.
TITLE       Nucleic acid encoding human aminopeptidase P.
JOURNAL     Patent: WO9911799-A2; Filing Date: 02-SEP-1998; 98WO-US018426;
          Publication Date: 11-MAR-1999; Priority: 02-SEP-1997;
          97US-0057854P; Assignee: (MEDI-) MEDICAL COLLEGE GEORGIA RES INST;
          Cross Reference: WPI; 1999-205193/17; Patent Format: Claim 13; Page
          109-139; 201pp; English.

COMMENT     This invention describes the isolation of a novel human
          aminopeptidase P (AmP). This protein is used to produce recombinant
          AmP and can be used for gene therapy for treating AmP-deficiency
          conditions. Its fragments are used as primers and probes to
          identify patients with homozygous and heterozygous AmP deficiency,
          including prenatal diagnosis (patients defective in AmP are at risk
          of developing angioedema if treated with angiotensin-converting
          enzyme inhibitors), also as antisense inhibitors in cases of
          excessive AmP expression. The product of the invention is also used
          to identify AmP-expressing sequences in other animals and to
          generate transgenic animals, and comparisons of genomic sequences
          are used to detect mutations. AmP inhibitors are potentially useful
          as antihypertensive agents and to prevent or treat arterial
          (re)stenosis or atherosclerosis. The structure of AmP is used to
          design synthetic substrates, e.g. for use in AmP assays. AmP, which

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hydrolyzes N-terminal imido bonds, can be used to degrade industrial protein feeds to free amino acids, to degrade proteinaceous wastes, as additives in enzyme formulations used to treat malabsorption syndrome and for studying its biological role. Antibodies against AmP are used in immunohistochemical methods to study AmP distribution

FEATURES Location/Qualifiers

BASE COUNT 12605 a 11725 c 11351 g 14317 t

ORIGIN

468 100 0.0

HS454M7 Human DNA sequence from clone RP3-454M7 on chromosome Xq25-26.3, complete sequence. 151152 bp, DNA, linear, PRI 05-JUN-2003

ACCESSION AL022162

VERSION AL022162.1 GI:3171881

KEYWORDS HTG.

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 151152)

AUTHORS Pavitt, R.

TITLE Direct Submission

JOURNAL Submitted (05-JUN-2003) Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire, CB10 1SA, UK. E-mail enquiries:

humquery@sanger.ac.uk Clone requests: clonerequest@sanger.ac.uk

COMMENT On Jun 2, 1998 this sequence version replaced gi:2969945.

----- Genome Center

Center: Wellcome Trust Sanger Institute

Center code: SC

Web site: <http://www.sanger.ac.uk>

Contact: humquery@sanger.ac.uk

During sequence assembly data is compared from overlapping clones. Where differences are found these are annotated as variations together with a note of the overlapping clone name. Note that the variation annotation may not be found in the sequence submission corresponding to the overlapping clone, as we submit sequences with only a small overlap as described above.

This sequence was finished as follows unless otherwise noted: all regions were either double-stranded or sequenced with an alternate chemistry or covered by high quality data (i.e., phred quality = 30); an attempt was made to resolve all sequencing problems, such as compressions and repeats; all regions were covered by at least one plasmid subclone or more than one M13 subclone; and the assembly was confirmed by restriction digest, except on the rare occasion of the clone being a YAC.

The following abbreviations are used to associate primary accession numbers given in the feature table with their source databases:

Em:, EMBL; Sw:, SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information on the WORMPEP database can be found at

http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence was generated from part of bacterial clone contigs of human

chromosome X, constructed by the Sanger Centre Chromosome X Mapping Group. Further information can be found at

<http://www.sanger.ac.uk/HGP/ChrX>

RP3-454M7 is from the library RPCI-3 constructed by the group of

Pieter de Jong. For further details see

<http://www.chori.org/bacpac/home.htm>

VECTOR: pCYPAC2

This sequence is the entire insert of clone RP3-454M7.

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FEATURES             Location/Qualifiers
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                        /mol_type="genomic DNA"
                        /db_xref="RZPD:RPCIP704M07454"
                        /db_xref="taxon:9606"
                        /chromosome="X"
                        /map="q25-26.3"
                        /clone="RP3-454M7"
                        /clone_lib="RPCI-3"
    gene               767..35998
                        /gene="OCRL1"
    mRNA               join(<767..877,1303..1392,2075..2195,2282..2443,
                        3992..4093,4621..4735,5826..5942,6041..6228,9214..9325,
                        10696..10805,12706..12841,18582..18692,19339..19504,
                        19759..19994,30444..30560,31621..31705,32328..32455,
                        33287..33398,33588..35998)
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                        /product="dJ454M7.1.1 (Lowe Oculocerebrorenal Syndrome)"
                        /note="variant 1
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                        Em:AA044611 Em:AA188493 Em:AA743649 Em:AA836673 Em:R67320
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                        Em:AA042798 Em:AA122019 Em:H53971 Em:W38961 Em:AA805220
                        Em:AA868822 Em:AA032176 Em:AA034374 Em:T84250 Em:N56932
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                        10696..10805,12706..12841,18582..18692,19339..19504,
                        19759..19994,27786..27809,30444..30560,31621..31705,
                        32328..32455,33287..33398,33588..33712)
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                        /codon_start=1
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                        19759..19994,30444..30560,31621..31705,32328..32455,
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repeat_region 7178..8315
/note="L1PA2 repeat: matches 5000..6146 of consensus"
repeat_region 11225..11294
/note="MER5B repeat: matches 109..178 of consensus"
repeat_region 11345..11657
/note="AluYb8 repeat: matches 1..310 of consensus"
repeat_region 11736..11797
/note="31 copies 2 mer tt 72% conserved"
repeat_region 12436..12562
/note="L2 repeat: matches 2579..2710 of consensus"
repeat_region 13276..13457
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repeat_region 14132..14206
/note="MIR repeat: matches 163..233 of consensus"
repeat_region 14207..14413
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repeat_region 14414..14548
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/note="AluYb8 repeat: matches 1..302 of consensus"
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/note="L1PA9 repeat: matches 5491..5829 of consensus"
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/note="2 copies 168 mer 78% conserved"
repeat_region 18772..18981
/note="MIR repeat: matches 6..242 of consensus"
repeat_region 18945..19005
/note="L2 repeat: matches 2648..2702 of consensus"
repeat_region 20349..20489
/note="MIR repeat: matches 1..150 of consensus"
repeat_region 20543..20697
/note="MER5A repeat: matches 22..188 of consensus"
repeat_region 21496..21830
/note="L1MC4 repeat: matches 7477..7849 of consensus"
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22894..22965
repeat_region /note="3 copies 24 mer 83% conserved"
24309..24606
repeat_region /note="AluSx repeat: matches 1..299 of consensus"
25081..25134
repeat_region /note="27 copies 2 mer ta 70% conserved"
25168..25193
repeat_region /note="13 copies 2 mer tg 100% conserved"
25262..25301
repeat_region /note="20 copies 2 mer tc 90% conserved"
25302..25642
repeat_region /note="L2 repeat: matches 2078..2419 of consensus"
26542..26704
repeat_region /note="MIR repeat: matches 1..160 of consensus"
26822..27057
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28330..28399
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30715..30819
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31196..31319
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37202..37675
repeat_region /note="L2 repeat: matches 1597..2041 of consensus"
37676..37990
repeat_region /note="AluJb repeat: matches 1..312 of consensus"
37991..38142
repeat_region /note="L2 repeat: matches 2041..2182 of consensus"
38143..38316
repeat_region /note="MER5A repeat: matches 3..189 of consensus"
38317..38464
repeat_region /note="L2 repeat: matches 2182..2419 of consensus"
38676..38801
repeat_region /note="MIR repeat: matches 11..134 of consensus"
38858..38984
repeat_region /note="MIR repeat: matches 123..257 of consensus"
39284..39886
repeat_region /note="L2 repeat: matches 2147..2748 of consensus"
39913..40014
repeat_region /note="MIR repeat: matches 175..262 of consensus"
40015..40311
repeat_region /note="AluSg repeat: matches 1..297 of consensus"
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repeat_region /note="MIR repeat: matches 14..175 of consensus"
40667..40774
repeat_region /note="L2 repeat: matches 2616..2702 of consensus"
40776..41088
repeat_region /note="AluSx repeat: matches 1..305 of consensus"
41528..41936
repeat_region /note="L2 repeat: matches 2267..2709 of consensus"
42180..42713
repeat_region /note="L1MB3 repeat: matches 5584..6153 of consensus"
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/note="AluSq repeat: matches 12..313 of consensus"
repeat_region 46208..46584
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/note="AluSg repeat: matches 1..302 of consensus"
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repeat_region 47611..47774
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/note="AluY repeat: matches 1..306 of consensus"
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/note="L2 repeat: matches 1906..2046 of consensus"
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/note="MER53 repeat: matches 1..188 of consensus"
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/note="LTR19B repeat: matches 59..140 of consensus"
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/note="3 copies 24 mer 93% conserved"
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repeat_region 50914..51068
/note="MIR repeat: matches 34..211 of consensus"
repeat_region 51124..51292
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repeat_region 51517..51587
/note="MER96 repeat: matches 105..175 of consensus"
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/note="MIR repeat: matches 68..213 of consensus"
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/note="MIR repeat: matches 2..258 of consensus"
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/note="MLT1I repeat: matches 292..410 of consensus"
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56404..56697
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repeat_region /note="L2 repeat: matches 2605..2730 of consensus"
57036..57226
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57817..58128
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58772..59030
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59040..59091
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59050..59118
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59465..59797
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61554..61833
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62011..62239
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62265..62379
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63472..63529
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64262..64313
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64330..64409
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64459..64631
repeat_region /note="L1MA10 repeat: matches 5999..6322 of consensus"
64637..64862
repeat_region /note="MER33 repeat: matches 5..225 of consensus"
65788..66082
repeat_region /note="AluJo repeat: matches 6..304 of consensus"
66968..66991
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67036..67653
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67654..67700
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67701..67998
repeat_region /note="AluY repeat: matches 1..296 of consensus"
67999..68463
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68464..68826
repeat_region /note="THE1B repeat: matches 1..364 of consensus"
68827..70335
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70349..70538
repeat_region /note="L2 repeat: matches 1697..1895 of consensus"
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repeat_region /note="AluY repeat: matches 1..305 of consensus"
70932..71126
repeat_region /note="L1ME3 repeat: matches 5734..5939 of consensus"

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repeat_region 71385..71690
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/note="MLT1F repeat: matches 11..513 of consensus"
repeat_region 72615..72631
/note="MIR repeat: matches 196..212 of consensus"
repeat_region 72632..72870
/note="MER8 repeat: matches 1..239 of consensus"
repeat_region 72871..73028
/note="MIR repeat: matches 45..196 of consensus"
repeat_region 73892..73979
/note="MIR repeat: matches 59..147 of consensus"
repeat_region 74431..74484
/note="27 copies 2 mer ca 96% conserved"
repeat_region 74436..74483
/note="2 copies 24 mer 100% conserved"
repeat_region 74504..74671
/note="MIR repeat: matches 2..171 of consensus"
repeat_region 75019..75185
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repeat_region 76554..76826
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repeat_region 76863..76903
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repeat_region 77089..77189
/note="MIR repeat: matches 41..144 of consensus"
repeat_region 77359..77679
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repeat_region 79058..79304
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/note="MIR repeat: matches 95..154 of consensus"
repeat_region 81526..81665
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repeat_region 81793..81843
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/note="L2 repeat: matches 2647..2722 of consensus"
repeat_region 82740..83045
/note="AluSx repeat: matches 1..312 of consensus"
repeat_region 83046..83071
/note="L2 repeat: matches 2722..2747 of consensus"
repeat_region 83813..83946
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repeat_region 83904..83954
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repeat_region /note="MIR repeat: matches 7..136 of consensus"
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               85012..85350
repeat_region /note="MLT1A2 repeat: matches 1..340 of consensus"
               85365..85456
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               85526..85776
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               86101..86173
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               87299..87643
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               88003..88303
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               92655..92799
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               99017..99109
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               99392..99521
repeat_region /note="L2 repeat: matches 2576..2710 of consensus"
               99694..99834
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               100093..100400
repeat_region /note="AluSx repeat: matches 3..312 of consensus"
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repeat_region /note="MER3 repeat: matches 3..207 of consensus"
               101144..101446
repeat_region /note="AluJo repeat: matches 1..292 of consensus"
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repeat_region /note="MIR repeat: matches 20..168 of consensus"
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repeat_region /note="MLT1A1 repeat: matches 1..51 of consensus"
               103053..103356
repeat_region /note="AluSp repeat: matches 1..303 of consensus"
               103357..103729
repeat_region /note="MLT1A1 repeat: matches 51..365 of consensus"
               103730..103791
repeat_region /note="MIR repeat: matches 168..231 of consensus"
               103886..103998
repeat_region /note="MSTA repeat: matches 1..114 of consensus"
               103996..104323
repeat_region /note="MSTA repeat: matches 1..388 of consensus"
               104372..104503
repeat_region /note="AluY repeat: matches 166..297 of consensus"
               104594..104824
repeat_region /note="MIR repeat: matches 10..259 of consensus"

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repeat_region 107333..107459
                /note="MLT1C repeat: matches 340..466 of consensus"
repeat_region 107460..107589
                /note="L1MA7 repeat: matches 6159..6288 of consensus"
repeat_region 107590..107718
                /note="MLT1C repeat: matches 211..340 of consensus"
repeat_region 107755..108017
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repeat_region 108019..108208
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repeat_region 108326..108922
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                /note="L1MA10 repeat: matches 5970..6317 of consensus"
repeat_region 110589..111071
                /note="L1ME1 repeat: matches 5477..5952 of consensus"
repeat_region 111077..111135
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repeat_region 111153..111414
                /note="L1MB3 repeat: matches 5909..6182 of consensus"
repeat_region 111419..111617
                /note="L1ME1 repeat: matches 5283..5487 of consensus"
repeat_region 111622..112876
                /note="L1MB8 repeat: matches 4877..6173 of consensus"
repeat_region 112873..114198
                /note="L1M4 repeat: matches 3073..4391 of consensus"
repeat_region 114206..115694
                /note="L1PA2 repeat: matches 4656..6144 of consensus"
repeat_region 115723..116219
                /note="MLT2CA repeat: matches 1..489 of consensus"
repeat_region 116220..116291
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repeat_region 116377..118409
                /note="L1MEc repeat: matches 1212..2985 of consensus"
repeat_region 118410..118683
                /note="AluY repeat: matches 1..298 of consensus"
repeat_region 118684..118923
                /note="L1MEc repeat: matches 983..1212 of consensus"
repeat_region 118955..119117
                /note="MER20 repeat: matches 51..218 of consensus"
repeat_region 119118..119284
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repeat_region 119285..119682
                /note="MLT1A1 repeat: matches 1..365 of consensus"
repeat_region 119683..119810
                /note="L1MEc repeat: matches 681..802 of consensus"
repeat_region 119830..120493
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repeat_region 120522..120894
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repeat_region    /note="MLT1B repeat: matches 1..426 of consensus"
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                  121180..121227
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                  121184..121227
repeat_region    /note="22 copies 2 mer gt 100% conserved"
                  122617..122772
repeat_region    /note="MER5A repeat: matches 4..188 of consensus"
                  122787..122900
repeat_region    /note="MER5B repeat: matches 91..173 of consensus"
                  122901..123193
repeat_region    /note="AluJo repeat: matches 4..298 of consensus"
                  123194..123275
repeat_region    /note="MER5B repeat: matches 1..91 of consensus"
                  123437..124087
repeat_region    /note="L2 repeat: matches 1555..2750 of consensus"
                  124164..124586
repeat_region    /note="L2 repeat: matches 57..485 of consensus"
                  125405..125535
repeat_region    /note="Charlie4a repeat: matches 369..495 of consensus"
                  125536..125695
repeat_region    /note="FRAM repeat: matches 2..161 of consensus"
                  125696..126026
repeat_region    /note="Charlie4a repeat: matches 19..369 of consensus"
                  126098..126459
repeat_region    /note="MLT1A1 repeat: matches 1..365 of consensus"
                  126630..126693
repeat_region    /note="L2 repeat: matches 2641..2704 of consensus"
                  126784..127362
repeat_region    /note="L2 repeat: matches 2176..2750 of consensus"
                  127366..127489
repeat_region    /note="MIR repeat: matches 46..185 of consensus"
                  127679..127826
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                  129216..129297
repeat_region    /note="L2 repeat: matches 2639..2710 of consensus"
                  129340..129554
repeat_region    /note="MIR repeat: matches 53..260 of consensus"
                  129661..129924
repeat_region    /note="MIR repeat: matches 2..261 of consensus"
                  131041..131232
repeat_region    /note="AluSg/x repeat: matches 135..292 of consensus"
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repeat_region 132996..133294
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repeat_region 134184..134313
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repeat_region 134373..134437
                /note="L1MA7 repeat: matches 6224..6288 of consensus"
repeat_region 134438..134744
                /note="MER2 repeat: matches 34..345 of consensus"
repeat_region 134748..134835
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repeat_region 134878..135187
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                /note="L1MD2 repeat: matches 5962..6340 of consensus"
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                /note="MIR repeat: matches 69..132 of consensus"
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                /note="MIR repeat: matches 12..206 of consensus"
repeat_region 137099..137227
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repeat_region 137228..137524
                /note="AluSx repeat: matches 1..296 of consensus"
repeat_region 137525..137870
                /note="MLT1D repeat: matches 130..471 of consensus"
repeat_region 137893..138056
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repeat_region 138057..138345
                /note="AluSx repeat: matches 5..292 of consensus"
repeat_region 138346..138472
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repeat_region 138474..138539
                /note="MLT1D repeat: matches 440..505 of consensus"
repeat_region 138554..138675
                /note="L2 repeat: matches 2066..2187 of consensus"
repeat_region 138694..139033
                /note="L2 repeat: matches 2362..2692 of consensus"
repeat_region 138993..139044
                /note="MIR repeat: matches 210..261 of consensus"
repeat_region 139737..139807
                /note="MLT1C repeat: matches 393..464 of consensus"
repeat_region 139808..139873
                /note="L1PA8 repeat: matches 6097..6162 of consensus"
repeat_region 139874..140272
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repeat_region 140332..140461
                /note="MER5A repeat: matches 26..189 of consensus"
repeat_region 140611..140903
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repeat_region 141410..141594
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repeat_region 142664..142699

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repeat_region /note="18 copies 2 mer to 100% conserved"
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 repeat_region /note="AluSc repeat: matches 1..278 of consensus"
 143097..143180
 repeat_region /note="L2 repeat: matches 2643..2749 of consensus"
 143339..143662
 repeat_region /note="MLT1A1 repeat: matches 6..365 of consensus"
 143783..143885
 repeat_region /note="L2 repeat: matches 2593..2702 of consensus"
 145806..145889
 repeat_region /note="MIR repeat: matches 37..130 of consensus"
 145957..146261
 repeat_region /note="AluSq repeat: matches 1..308 of consensus"
 146264..146376
 repeat_region /note="MIR repeat: matches 117..235 of consensus"
 147583..147657
 repeat_region /note="L2 repeat: matches 2422..2502 of consensus"
 147859..147978
 repeat_region /note="L2 repeat: matches 2616..2750 of consensus"
 148013..148084
 repeat_region /note="L2 repeat: matches 2636..2707 of consensus"
 148687..149141
 repeat_region /note="LTR16B repeat: matches 1..461 of consensus"
 150442..151102
 repeat_region /note="L2 repeat: matches 1490..2109 of consensus"

BASE COUNT
 ORIGIN

468 100 0.0

AF195953 Homo sapiens membrane-bound aminopeptidase P (XNPEP2) gene,
 complete cds. 206618 bp, DNA, linear, PRI 26-MAR-2002

ACCESSION AF195953

VERSION AF195953.2 GI:19718557

KEYWORDS

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
 Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 206618)

AUTHORS Ryan, J.W., Jin, L., Horvath, I. and Sprinkle, T.J.C.

TITLE Human membrane-bound aminopeptidase P genomic DNA

JOURNAL Unpublished

REFERENCE 2 (bases 1 to 206618)

AUTHORS Ryan, J.W., Jin, L., Horvath, I. and Sprinkle, T.J.C.

TITLE Direct Submission

JOURNAL Submitted (18-OCT-1999) Vascular Biology Center, Medical College of
 Georgia, 1120 15th Street, Augusta, GA 30912, USA

REFERENCE 3 (bases 1 to 206618)

AUTHORS Ryan, J.W., Jin, L., Horvath, I. and Sprinkle, T.J.C.

TITLE Direct Submission

JOURNAL Submitted (26-MAR-2002) Vascular Biology Center, Medical College of
 Georgia, 1120 15th Street, Augusta, GA 30912, USA

REMARK Sequence update by submitter

COMMENT On Mar 26, 2002 this sequence version replaced gi:11066156.

FEATURES Location/Qualifiers

source 1..206618

/organism="Homo sapiens"

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        /mol_type="genomic DNA"
        /db_xref="taxon:9606"
gene     144189..176791
        /gene="XNPEP2"
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150445..150508,151478..151582,151837..151923,
152849..152995,155710..155811,156987..157068,
157392..157587,158401..158490,159714..159823,
160536..160613,161726..161797,164422..164482,
165754..165823,166414..166518,167248..167307,
167936..168012,172845..172934,173533..176791)
        /gene="XNPEP2"
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5'UTR    144189..144453
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152849..152995,155710..155811,156987..157068,
157392..157587,158401..158490,159714..159823,
160536..160613,161726..161797,164422..164482,
165754..165823,166414..166518,167248..167307,
167936..168012,172845..172934,173533..173727)
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        /db_xref="GI:11066157"
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        /note="putative proton shuttle; unclassified site"
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        /note="divalent metal ligand; metal-binding site"
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        /note="divalent metal ligand; metal-binding site"
misc_feature 167977..167979
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3'UTR    175728..176791
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BASE COUNT
ORIGIN

467 99 0.0

P_AAH14799 Human cDNA sequence SEQ ID NO:12589. 243 bp, cDNA, PAT 26-JUN-2001

ACCESSION P_AAH14799

KEYWORDS GENESEQ; Human; primer; detection; diagnosis; antisense therapy;
gene therapy; patent; patentdb (v200414, 01-JUL-2004).

SOURCE Homo sapiens.

ORGANISM Homo sapiens.

REFERENCE 1 (bases 1 to 2243)

AUTHORS Ota,T., Isogai,T., Nishikawa,T., Hayashi,K., Saito,K., Yamamoto,J. Ishii,S., Sugiyama,T., Wakamatsu,A., Nagai,K., Otsuki,T.

TITLE Primer sets for synthesizing polynucleotides, particularly the 5602 full- length cDNAs defined in the specification, and for the detection and/or diagnosis of the abnormality of the proteins encoded by the full-length cDNAs.

JOURNAL Patent: EP1074617-A2; Filing Date: 28-JUL-2000; 2000EP-00116126; Publication Date: 07-FEB-2001; Priority: 29-JUL-1999; 99JP-00248036. 27-AUG-1999; 99JP-00300253. 11-JAN-2000; 2000JP-00118776. 02-MAY-2000; 2000JP-00183767. 09-JUN-2000; 2000JP-00241899; Assignee: (HELI-) HELIX RES INST; Cross Reference: WPI; 2001-318749/34; Patent Format: Claim 8; SEQ ID NO 12589; 2537pp + Sequence Listing; English.

COMMENT The present invention describes primer sets for synthesising 5602 full- length cDNAs defined in the specification. Where a primer set comprises: (a) an oligo-dT primer and an oligonucleotide complementary to the complementary strand of a polynucleotide which comprises one of the 5602 nucleotide sequences defined in the specification, where the oligonucleotide comprises at least 15 nucleotides; or (b) a combination of an oligonucleotide comprising a sequence complementary to the complementary strand of a polynucleotide which comprises a 5'-end sequence and an oligonucleotide comprising a sequence complementary to a polynucleotide which comprises a 3'-end sequence, where the oligonucleotide comprises at least 15 nucleotides and the combination of the 5'-end sequence/3'-end sequence is selected from those defined in the specification. The primer sets can be used in antisense therapy and in gene therapy. The primers are useful for synthesising polynucleotides, particularly full-length cDNAs. The primers are also useful for the detection and/or diagnosis of the abnormality of the proteins encoded by the full-length cDNAs. The primers allow obtaining of the full-length cDNAs easily without any specialised methods. AAH03166 to AAH13628 and AAH13633 to AAH18742 represent human cDNA sequences; AAB92446 to AAB95893 represent human amino acid sequences; and AAH13629 to AAH13632 represent oligonucleotides, all of which are used in the exemplification of the present invention

FEATURES Location/Qualifiers
BASE COUNT 467 a 630 c 637 g 509 t
ORIGIN

467 99 0.0

AK001855 Homo sapiens cDNA FLJ10993 fis, clone PLACE1002140. 2243 bp, mRNA, linear, PRI 30-JAN-2004

ACCESSION AK001855

VERSION AK001855.1 GI:7023382

KEYWORDS oligo capping; fis (full insert sequence).

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1

AUTHORS Ota,T., Suzuki,Y., Nishikawa,T., Otsuki,T., Sugiyama,T., Irie,R., Wakamatsu,A., Hayashi,K., Sato,H., Nagai,K., Kimura,K., Makita,H., Sekine,M., Obayashi,M., Nishi,T., Shibahara,T., Tanaka,T.,

Ishii, S., Yamamoto, J., Saito, K., Kawai, Y., Isono, Y., Nakamura, Y., Nagahari, K., Murakami, K., Yasuda, T., Iwayanagi, T., Wagatsuma, M., Shiratori, A., Sudo, H., Hosoiri, T., Kaku, Y., Kodaira, H., Kondo, H., Sugawara, M., Takahashi, M., Kanda, K., Yokoi, T., Furuya, T., Kikkawa, E., Omura, Y., Abe, K., Kamihara, K., Katsuta, N., Sato, K., Tanikawa, M., Yamazaki, M., Ninomiya, K., Ishibashi, T., Yamashita, H., Murakawa, K., Fujimori, K., Tanai, H., Kimata, M., Watanabe, M., Hiraoka, S., Chiba, Y., Ishida, S., Ono, Y., Takiguchi, S., Watanabe, S., Yosida, M., Hotuta, T., Kusano, J., Kanehori, K., Takahashi-Fujii, A., Hara, H., Tanase, T., Nomura, Y., Togiya, S., Komai, F., Hara, R., Takeuchi, K., Arita, M., Imose, N., Musashino, K., Yuuki, H., Oshima, A., Sasaki, N., Aotsuka, S., Yoshikawa, Y., Matsunawa, H., Ichihara, T., Shiohata, N., Sano, S., Moriya, S., Momiyama, H., Satoh, N., Takami, S., Terashima, Y., Suzuki, O., Nakagawa, S., Senoh, A., Mizoguchi, H., Goto, Y., Shimizu, F., Wakebe, H., Hishigaki, H., Watanabe, T., Sugiyama, A., Takemoto, M., Kawakami, B., Yamazaki, M., Watanabe, K., Kumagai, A., Itakura, S., Fukuzumi, Y., Fujimori, Y., Komiyama, M., Tashiro, H., Tanigami, A., Fujiwara, T., Ono, T., Yamada, K., Fujii, Y., Ozaki, K., Hirao, M., Ohmori, Y., Kawabata, A., Hikiji, T., Kobatake, N., Inagaki, H., Ikema, Y., Okamoto, S., Okitani, R., Kawakami, T., Noguchi, S., Itoh, T., Shigeta, K., Senba, T., Matsumura, K., Nakajima, Y., Mizuno, T., Morinaga, M., Sasaki, M., Togashi, T., Oyama, M., Hata, H., Watanabe, M., Komatsu, T., Mizushima-Sugano, J., Satoh, T., Shirai, Y., Takahashi, Y., Nakagawa, K., Okumura, K., Nagase, T., Nomura, N., Kikuchi, H., Masuho, Y., Yamashita, R., Nakai, K., Yada, T., Nakamura, Y., Ohara, O., Isogai, T. and Sugano, S.

TITLE Complete sequencing and characterization of 21,243 full-length human cDNAs

JOURNAL Nat. Genet. 36 (1), 40-45 (2004)

PUBMED 14702039

REFERENCE 2

AUTHORS Isogai, T., Ota, T., Hayashi, K., Sugiyama, T., Otsuki, T., Suzuki, Y., Nishikawa, T., Nagai, K., Sugano, S., Takahashi-Fujii, A., Hara, H., Tanase, T., Nomura, Y., Togiya, S., Komai, F., Hara, R., Takeuchi, K., Arita, M., Nabekura, T., Ishii, S., Kawai, Y., Saito, K., Yamamoto, J., Wakamatsu, A., Nakamura, Y., Nagahari, K., Masuho, Y. and Oshima, A.

TITLE NEDO human cDNA sequencing project

JOURNAL Unpublished

REFERENCE 3 (bases 1 to 2243)

AUTHORS Isogai, T. and Otsuki, T.

TITLE Direct Submission

JOURNAL Submitted (16-FEB-2000) Takao Isogai, Helix Research Institute, Genomics Laboratory; 1532-3 Yana, Kisarazu, Chiba 292-0812, Japan (E-mail:genomics@hri.co.jp, Tel:81-438-52-3975, Fax:81-438-52-3986)

COMMENT NEDO human cDNA sequencing project supported by Ministry of International Trade and Industry of Japan; cDNA full insert sequencing: Research Association for Biotechnology; cDNA library construction, 5'- & 3'-end one pass sequencing and clone selection: Helix Research Institute (supported by Japan Key Technology Center etc.) and Department of Virology, Institute of Medical Science, University of Tokyo.

FEATURES Location/Qualifiers

source

1..2243

/organism="Homo sapiens"

/mol_type="mRNA"

/db_xref="taxon:9606"

/clone="PLACE1002140"

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/tissue_type="placenta"
/clone_lib="PLACE1"
/note="cloning vector: pME18SFL3"
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    /note="unnamed protein product"
    /codon_start=1
    /protein_id="BAA91944.1"
    /db_xref="GI:7023383"

BASE COUNT
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449  98   0.0
AX332625   Sequence 3134 from Patent WO0194629. 458 bp,
          DNA, linear, PAT 09-JAN-2002
ACCESSION   AX332625
VERSION     AX332625.1  GI:18123259
KEYWORDS    .
SOURCE      Homo sapiens (human)
            ORGANISM Homo sapiens
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
              Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
AUTHORS     Young,P.E., Augustus,M., Carter,K.C., Ebner,R., Endress,G.,
            Horrigan,S., Soppet,D.R. and Weaver,Z.
TITLE       Cancer gene determination and therapeutic screening using signature
            gene sets
JOURNAL     Patent: WO 0194629-A 3134 13-DEC-2001;
            Avalon Pharmaceuticals (US)
FEATURES    Location/Qualifiers
            source          1..458
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                        /mol_type="unassigned DNA"
                        /db_xref="taxon:9606"

BASE COUNT
ORIGIN

449  98   0.0
AX332852   Sequence 3361 from Patent WO0194629. 458 bp,
          DNA, linear, PAT 09-JAN-2002
ACCESSION   AX332852
VERSION     AX332852.1  GI:18123486
KEYWORDS    .
SOURCE      Homo sapiens (human)
            ORGANISM Homo sapiens
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
              Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
AUTHORS     Young,P.E., Augustus,M., Carter,K.C., Ebner,R., Endress,G.,
            Horrigan,S., Soppet,D.R. and Weaver,Z.
TITLE       Cancer gene determination and therapeutic screening using signature
            gene sets
JOURNAL     Patent: WO 0194629-A 3361 13-DEC-2001;
            Avalon Pharmaceuticals (US)
FEATURES    Location/Qualifiers
            source          1..458
                        /organism="Homo sapiens"
                        /mol_type="unassigned DNA"

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/db_xref="taxon:9606"

BASE COUNT
ORIGIN

Dayhoff Protein Database (Rel 78, Mar 2004)

P_AAB87540 Human PRO831 - Homo sapiens.

Length: 73 aa

Accession: P_AAB87540;

Species: Homo sapiens.

Keywords: Human; PRO protein; mapping; patent; GENESEQ patentdb.

Patent number: WO200116318-A2.

Publication date: 08-MAR-2001.

Filing date: 24-AUG-2000; 2000WO-US023328.

Priority: 01-SEP-1999; 99WO-US020111. 15-SEP-1999; 99WO-US021090.

07-DEC-1999; 99US-0169495P. 09-DEC-1999; 99US-0170262P.

11-JAN-2000; 2000US-0175481P. 18-FEB-2000; 2000WO-US004341.

18-FEB-2000; 2000WO-US004342. 22-FEB-2000; 2000WO-US004414.

01-MAR-2000; 2000WO-US005601. 03-MAR-2000; 2000US-0187202P.

21-MAR-2000; 2000US-0191007P. 30-MAR-2000; 2000WO-US008439.

25-APR-2000; 2000US-0199397P. 22-MAY-2000; 2000WO-US014042.

05-JUN-2000; 2000US-0209832P.

Assignee: (GETH) GENENTECH INC.

Inventors: Eaton DL, Filvaroff E, Gerritsen ME, Goddard A, Godowski PJ;
Grimaldi CJ, Gurney AL, Watanabe CK, Wood WI;

Cross reference: WPI; 2001-183260/18. N-PSDB; AAF92072.

Title: Eighty four nucleic acids encoding PRO polypeptides, useful in molecular biology, including use as hybridization probes, and in chromosome and gene mapping.

Patent format: Claim 12; Fig 30; 278pp; English.

Comment: The present sequence is a human PRO polypeptide (secreted and transmembrane). The PRO protein, and PRO agonists, PRO antagonists or anti-PRO antibodies are useful for preparation of a medicament useful in the treatment of a condition which is responsive to the PRO protein, agonists, antagonists or anti-PRO antibodies. The PRO protein may also be employed as molecular weight markers for protein electrophoresis. The PRO coding sequence has applications in molecular biology, including use as hybridisation probes, and in chromosome and gene mapping

Database: GENESEQ patent database (v200414, 01-JUL-2004).

P_AAY99346 Human PRO831 (UNQ471) amino acid sequence SEQ ID NO:22 - Homo sapiens.

Length: 73 aa

Accession: P_AAY99346;

Species: Homo sapiens.

Keywords: Human; PRO polypeptide; membrane bound protein; receptor;
diagnosis; transmembrane; secretion; immunoadhesion;
pharmaceutical; screening; patent; GENESEQ patentdb.

Patent number: WO200012708-A2.

Publication date: 09-MAR-2000.

Filing date: 01-SEP-1999; 99WO-US020111.

Priority: 01-SEP-1998; 98US-0098716P. 01-SEP-1998; 98US-0098749P.

01-SEP-1998; 98US-0098750P. 18-NOV-1998; 98US-0108858P. 18-NOV-1998;

98US-0108904P. plus 119 more dates.

Assignee: (GETH) GENENTECH INC.

Inventors: Baker K, Goddard A, Gurney AL, Smith V, Watanabe CK, Wood WI;

Cross reference: WPI; 2000-237871/20. N-PSDB; AAA37028.

Title: New mammalian DNA sequences encoding transmembrane, receptor or secreted PRO polypeptides, useful for screening of potential peptide or small molecule inhibitors of the relevant

receptor/ligand interactions.

Patent format: Claim 12; Fig 14; 773pp; English.

Comment: AAA37022 to AAA37144 encode the new isolated human transmembrane, receptor or secreted PRO polypeptides given in AAY99340 to AAY99462. The transmembrane and receptor PRO proteins can be used for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interactions. The polypeptides and nucleotide sequences encoding then have various industrial applications, including uses as pharmaceutical and diagnostic agents. AAA37145 to AAA37330 represent PCR primers and hybridisation probes used in the isolation of the PRO polypeptides from the present invention

Database: GENESEQ patent database (v200414, 01-JUL-2004).